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DRUG SAFETY

Safety profile of the direct oral anticoagulants: an analysis of the WHO database of adverse drug reactions

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AIM

Direct oral anticoagulants (DOACs) have shown noninferiority to warfarin for stroke prevention in nonvalvular atrial fibrillation (AF) and a more promising safety profile. Unanswered safety aspects remain to be addressed and available evidence on the risk associated with these drugs are conflicting. In order to contribute to the debate on their safety profile, we conducted a comparative analysis of the reports of suspected adverse drug reactions (ADRs) associated with DOACs in VigiBase.

METHODS

Study based on reports of suspected ADRs held in VigiBase as at December 2014, in which a DOAC or warfarin were administered in patients with nonvalvular AF and listed as suspected/interacting drugs. Medical Dictionary for Regulatory Activities was used to classify ADRs. Reporting odds ratio (ROR) with 95% confidence interval were calculated. Results with $P \leq 0.05$ were statistically significant.

RESULTS

We retrieved 32 972 reports. We identified 204 ADRs with a ROR >1 ($P \leq 0.05$) and we focused on 105 reactions. Positive ROR emerged for DOACs and *gastrointestinal haemorrhage* compared with warfarin [(1.6 (1.47–1.75)], but no disproportionality with *cerebral haemorrhage* was found [0.31 (0.28–0.34)]. We identified other potential signals that have not been associated with DOACs previously.

CONCLUSIONS

As well as premarketing authorization clinical trial studies, we found a reduced risk of intracranial haemorrhage, but an increased risk of gastrointestinal haemorrhage in patients treated with DOACs compared to warfarin. We provide new data and we highlight several differences between the three novel oral anticoagulants, in the rate and type of ADRs occurred

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Dabigatran, rivaroxaban and apixaban have shown noninferiority to warfarin for stroke prevention in nonvalvular atrial fibrillation.
- Data on the comparative safety profile of direct oral anticoagulants (DOACs) and warfarin are conflicting.
- A comparative disproportionality analysis of the reports of suspected adverse drug reactions (ADRs) associated with DOACs in VigiBase was performed.

WHAT THIS STUDY ADDS

- Data regarding the risk of DOAC-induced haemorrhage are consistent with most studies.
- New ADRs not previously associated with DOACs were identified and they deserve further analysis.
- Our data suggest that DOACs are not interchangeable, as several differences emerged in the rate and type of ADRs between one drug and another.

Tables of Links

TARGETS	
Vitamin K Epoxide Reductase	Coagulation Factor II
Coagulation Factor X	

LIGANDS	
Apixaban	Dabigatran
Idarucizumab	Rivaroxaban
Warfarin	

These Tables list key protein targets and ligands in this article that are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [1], and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 [2].

Introduction

Vitamin K antagonists (VKAs) such as warfarin, have been the mainstay of oral anticoagulation for decades, being the preferred option to prevent stroke or systemic embolism events in patients with atrial fibrillation (AF), which is the most common cardiac arrhythmia in the general population, with a prevalence of 1–3%, (up to 15% in the elderly) [3].

In recent years, new oral anticoagulants, to which we will refer as direct oral anticoagulants or DOACs, as recommended by International Society on Thrombosis and Haemostasis, have been approved [4]. These novel agents, with direct inhibition of factor IIa (dabigatran) or Xa (rivaroxaban, apixaban), have shown noninferiority or superiority to warfarin for stroke prevention in AF and a more promising safety profile with respect to the important outcome of bleeding [5–7].

DOACs also seem to offer several advantages over warfarin, including rapid onset of action, few drug and food interactions and predictable pharmacokinetics, apparently eliminating the requirement for regular coagulation monitoring [8]. However, their use is still limited by some concerns about medication adherence without laboratory monitoring, dosing in certain group of patients, absence of specific antidotes for rivaroxaban and apixaban and higher drug costs compared with warfarin.

Some unanswered safety aspects remain to address and postmarketing data on the risks associated with these novel agents are conflicting.

A meta-analysis of randomized trials involving patients with AF receiving DOACs or warfarin showed that DOACs significantly reduced intracranial haemorrhage and mortality, with major bleeding similar to warfarin, but increased gastrointestinal bleeding [9]. A meta-analysis by Chatterjee *et al*. focused on the risk of intracranial haemorrhage came to the same conclusion [10], while another found that DOACs were associated with a lower risk of intracranial haemorrhage but not with a risk of gastrointestinal bleeding compared to warfarin. Moreover, the combined result of high-dose and low-dose regimens determined that DOACs were associated with lower risk of major bleeding events [11].

A study focusing on older Medicare patients with nonvalvular AF found an increased risk of gastrointestinal bleeding with dabigatran compared to warfarin [12].

Conversely, in a cohort study, neither dabigatran nor rivaroxaban were associated with a statistically increased risk of gastrointestinal bleeding relative to warfarin [13]. Other observational studies identified no differences in the rates of gastrointestinal bleeding for both newer agents, although the risk for patients significantly increased over the age of 65 years, and, by age 75 years, the risk exceeded that with warfarin [14].

As far as the risk of myocardial infarction or acute coronary syndrome is concerned, in a meta-analysis by Uchino and colleagues, dabigatran was associated with an increased risk of these events in a broad spectrum of patients when tested against different controls [15]. A subsequent meta-analysis confirmed these findings, adding that the increased risk is shared by other oral direct thrombin inhibitors [16].

Another safety aspect closely monitored for DOACs concerns the possible onset of drug-induced liver injury. A meta-analysis published in 2014 showed that DOACs did not increase the risk of this serious ADR [17]. Conversely, Liakoni *et al*. found that reports of liver injury associated with DOACs has been described in case reports, clinical studies and in the spontaneous reporting database of the World Health Organization (WHO) [18].

In order to contribute real-life data to the debate on the safety profiles of DOACs, we aimed to conduct a comparative analysis of the reports of suspected adverse drug reactions (ADRs) associated with the use of these drugs in the database of the WHO.

Methods

We obtained all the ADR reports held in VigiBase on 2nd December 2014 in which novel oral anticoagulants (apixaban, rivaroxaban, dabigatran) or warfarin were listed as suspected/interacting drugs: concomitant drugs were excluded. VigiBase is maintained by the Uppsala Monitoring Centre (Uppsala, Sweden) and contains national data on ADR reports from over 110 countries (December 2015) [19]. Starting from 1968, the centre has received summary clinical reports about individual suspected ADRs from the national centres of the countries participating in the collaborative program (in Italy, the Italian Medicines Agency). The participating countries may access and analyse the data in order to investigate potential ADR signals.

For our purpose, we eliminated all the reports having missing data in the field of the suspect/interacting drug or in that of Medical Dictionary for Regulatory Activities (MedDRA) preferred term. ADRs were coded according to the MedDRA, a standardized medical terminology to facilitate sharing of regulatory information internationally for medical products used by humans [20].

In order to detect and exclude as many duplicates as possible in the database, we performed an analysis using a record-linkage strategy by grouping the overlapping records in three key fields: report_id (i.e. the unique number identifying each case report), preferred-base-name, MeddraPtCode.

We compared the safety profile of DOACs versus warfarin, using the reporting odds ratio (ROR) as a measure of disproportionality. This is a quantitative approach based on frequency analyses of 2×2 contingency tables, aimed at evaluating if the observed number of reports for a specific drug–reaction combination (i.e. drug–reaction pairs or cases) is greater than the other ones resulting from the whole database (i.e. 'expected' or controls) [21]. ROR >1 indicate that a specific drug is likely to have more frequent reporting of a given ADR than any other drug. We estimated the ROR and 95% CI for each drug–reaction pair considered, and a safety signal was identified if a specific drug–ADR combination was reported more than twice with a ROR > 1. Results were considered statistically significant at a P value ≤0.05.

Data management and statistical analysis were carried out using the SPSS 21.0 statistical package (SPSS Inc., Chicago, IL, USA). For each drug with a significantly positive ROR, we verified whether the corresponding MedDRA preferred term was acknowledged in the Summary of Product Characteristics (SmPCs) made available by the European Medicines Agency, US Food and Drug Administration or Electronic Medicines Compendium. We statistically analysed both the pooled data and the individual drugs, and among drug–reaction pairs with significant RORs, we conducted a careful assessment based on the number of cases, the notoriety and the potential clinical risk of the reaction.

Results

Descriptive analysis

Up to December 2014 we retrieved a total number of 115 412 Individual Case Safety Reports (ICSRs) referred to DOACs or warfarin, of which 32 972 (28.6%) cases were related to patients with nonvalvular AF. Focusing on these reports, 51% concerned dabigatran, 28% warfarin, 19% rivaroxaban and 2% apixaban. In 27 297 cases (83%) the anticoagulant was the only drug reported as suspected.

Small difference emerged between males and females (51% and 46% respectively), while the information about sex was not available in the remaining cases; the average age of patients was 75.6 years (±10.1).

Table 1 shows reports classified as serious (69%), not serious (29%) and not available information (2%), and further broken down by sex and age class; as expected, most of serious cases occurred in the elderly men (32%, 7275 cases out of 22 724). Among serious cases, 3189 (9.7%) had a fatal outcome.

We applied the same classification to describe the seriousness criteria of ADRs reported on ICSRs, and most of them caused or prolonged the hospitalization of patients. An in-depth focus on how these criteria were divided among our study population, is provided in the supplemental material (Table S1).

ICSRs under analysis derived from USA (60%), Germany (9%), Italy (8%), UK (3%), Canada, Japan and Norway (about 2%, each).

Disproportionality analysis

We collected 3230 drug-reaction pairs and, among these, 204 had a ROR >1. We analysed 105 reactions, according to their statistical and clinical relevance (Table 2). The top five MedDRA system organ classes were gastrointestinal disorders (15% of ADRs), cardiac disorders (13%), investigations (12%), nervous system disorders and musculoskeletal and connective tissue disorders (11%).

The most reported DOAC was dabigatran, which resulted statistically significant in 77% of 105 drug-reaction pairs, followed by rivaroxaban (67%) and apixaban (36%).

Among selected statistically significant ADRs, gastrointestinal haemorrhage mostly occurred for dabigatran (1707 cases) and rivaroxaban (541 cases), while apixaban was mostly associated with cerebrovascular accident (16 cases; Tables S2–S4). Table S5 shows the number of cases of ADRs significantly associated with DOACs (ROR >1, $P \leq 0.05$) compared to warfarin.

Both rivaroxaban and dabigatran showed positive ROR for gastrointestinal haemorrhage compared to warfarin, respectively with 1.38 (1.24–1.55) and 1.71 (1.56–1.87); apixaban ROR was 0.95 (0.65–1.39).

Table 1

Population characteristics and serious cases (as indicated into the Individual Case Safety Report) related to age category and sex

Age class	Reports (*n*)			Serious			Not serious			Not available		
	F	M	NA	F	M	NA	F	M	NA	F	M	NA
0–23 months (infants/newborns)	2	2	0	2	2	0	0	0	0	0	0	0
2–17 years (children/teens)	3	7	0	2	6	0	1	0	0	0	1	0
18–64 years (adults)	875	1785	20	617	1370	18	215	365	2	43	50	0
≥ 65 years (elderly)	8406	9148	143	6219	7275	127	1908	1605	14	279	268	2
Not available	5943	5843	795	3160	3297	629	2776	2539	158	7	7	8
Partial	15 229	16 785	958	10 000	11 950	774	4900	4509	174	329	326	10
Total	32 972 (100%)			22 724 (69%)			9583 (29%)			665 (2%)		

F, female; M, male; NA, not available.

DOACs showed an inverse causal association with cerebral haemorrhage compared to warfarin [ROR 0.31 (0.28–0.34)] whereas for intracranial haemorrhage (ICH) the figure was not significant [1.05 (0.89–1.25)]. However, considering rivaroxaban only, a positive association with ICH was detected [1.65 (1.35–2.03)].

As shown in Table S6, many others ADRs were associated with an inverse disproportionality (ROR <1, $P \leq 0.05$), supporting the literature data in which a minor risk for DOACs has been found.

Significant disproportionality emerged for DOACs associated with cardiac failure [3.17 (2.02–4.96)], deep vein thrombosis [4.73 (3.02–7.41)], pulmonary embolism [6.03 (3.73–9.75)] and rivaroxaban with myocardial infarction [2.09 (1.31–3.32)]. The pooled analysis showed that DOACs were associated with angina pectoris [2.62 (1.17–5.87)], albeit ROR reached statistical significance only for rivaroxaban [3.28 (1.31–8.22)] and dabigatran [2.35 (1.01–5.45)].

The association between disseminated intravascular coagulation and dabigatran was statistically significant [12.67 (3.05–52.57)], being the suspected drug in about 90% of cases.

A considerable number of nervous system disorders related to the novel anticoagulants (particularly dabigatran and rivaroxaban) emerged from our analysis: cerebrovascular accident [5.19 (4.16–6.48)], ischaemic stroke [10.29 (6.02–17.6)], transient ischaemic attack [3.11 (2.25–4.31)], cerebral infarction [6.82 (3.96–11.72)] and embolic stroke [6.63 (3.49–12.6)].

As for hepatotoxicity, we observed significant RORs for hepatic failure associated with rivaroxaban and dabigatran [3.88 (1.84–8.21), 2.05 (1004–4.2), respectively]; no cases were reported for apixaban. Hepatitis resulted statistically significant with rivaroxaban [10.59 (2.37–47.33)] and apixaban [35.49 (5.93–212.62)], albeit confidence intervals were broad.

We found potential signals referred to DOACs and arthralgia [3.55 (2.72–4.63)], and joint swelling [5.81 (3.49–9.68)]; also, dabigatran and rivaroxaban were associated with myalgia [2.45 (1.59–3.79), 2.51 (1.52–4.15), respectively] and muscular weakness [2.4 (1.46–3.94), 2.83 (1.62–4.94)]. Dabigatran resulted associated with muscle spasms [2.71(1.73–4.25)].

Other potential signals of interest for all DOACs were visual impairment [4.84 (2.44–9.6)] and blindness [4.51 (1.37–14.83)], dabigatran-associated sepsis and hip fracture [1.94 (1.23–3.07) and 5.48 (2.16–13.88), respectively)].

Discussion

To our knowledge, this is the first study comparing the safety profile of DOACs *vs.* warfarin (as a class and individual drugs) based on data of daily clinical practice, in patients with nonvalvular AF.

Generally, our findings are consistent with those of premarketing authorization clinical trial studies, which showed a reduced risk of intracranial haemorrhage, but an increased risk of gastrointestinal haemorrhage [9].

Taking into account all DOACs, the pooled analysis showed no positive association with nervous system haemorrhage relative to warfarin. While the individual assessment of dabigatran or apixaban remained nonsignificant, the result about rivaroxaban was equivocal, as we detected a statistically significant association with ICH. Results from the rivaroxaban ROCKET-AF pivotal study highlighted a significant reduction of ICH risk against warfarin [7], but information from a real-life setting are still conflicting and, in this context, our finding could be noteworthy. Several cases of intracerebral bleeding associated with rivaroxaban have been reported in literature from post-marketing daily practice [22–26]. A retrospective matched-cohort study on US Symphony Health Solutions database found that the real-world safety for ICH was not statistically different for rivaroxaban and warfarin users [Hazard Ratio 1.17 (0.66–2.05)] [27].

A recent meta-analysis based on 25 RCTs and 24 nonrandomized studies, highlighted that rivaroxaban had less benefit in reducing ICH compared to other DOACs [28].

Our results confirmed the increased tendency of novel anticoagulants to develop gastrointestinal bleeding compared to warfarin, especially for dabigatran and rivaroxaban. Various results from several studies have been reported so far. Some authors attributed this variability to differences in number of patients enrolled for each study, in their age, in

Table 2

Adverse drug reactions (ADRs) statistically associated with direct oral anticoagulants [DOACs; reporting odds ratio (ROR) >1, p value ≤ 0.05] compared to warfarin (overall and individual comparison) and notoriety[a]

MedDRA system organ class[b]	MedDRA preferred term	DOACs ROR	Rivaroxaban ROR	Apixaban ROR	Dabigatran ROR	Notoriety		
						Rivaroxaban	Apixaban	Dabigatran
	Peripheral artery thrombosis	4.83 (1.13–20.67)			5.48 (1.26–23.82)	N	N	N
Blood	DIC	9.91 (2.4–40.96)			12.67 (3.05–52.57)	N	N	N
Blood	Haemorrhagic anaemia	1.35 (1.03–1.78)	1.89 (1.37–2.63)			Y	Y	Y
Blood	Haemorrhagic diathesis	3.62 (1.28–10.29)	7.95 (2.69–23.48)			Y	Y	Y
Blood	Thrombocytopenia	1.43 (1.01–2.01)	1.89 (1.25–2.85)	3.23 (1.37–7.59)		Y	Y	Y
Card	Acute myocardial infarction	2.84 (1.7–4.76)			3.39 (2.01–5.7)	N	N	Y
Card	Angina pectoris	2.62 (1.17–5.87)	3.28 (1.31–8.22)		2.35 (1.01–5.45)	Y	N	N
Card	Atrial fibrillation	1.3 (1.07–1.59)			1.38 (1.12–1.7)	N	N	N
Card	Atrial flutter	2.98 (1.26–7.06)	2.94 (1.07–8.09)		2.97 (1.22–7.21)	N	N	N
Card	Cardiac disorder	2.9 (1.22–6.88)			2.97 (1.22–7.21)	Y	N	Y
Card	Cardiac failure	3.17 (2.02–4.96)	3.45 (2.07–5.78)	4.3 (1.48–12.51)	3.02 (1.9–4.8)	N	N	N
Card	Cardiac tamponade	2.71 (1.5–4.9)	2.85 (1.43–5.7)		2.74 (1.49–5.03)	N	N	N
Card	Cardiogenic shock	3.54 (1.06–11.84)			4.11 (1.21–13.94)	Y	N	N
Card	Intracardiac thrombus	5.61 (2.25–13.98)	6.71 (2.51–17.97)		5.2 (2.05–13.22)	N	N	N
Card	Myocardial infarction	2.79 (1.92–4.03)	2.09 (1.31–3.32)		3.14 (2.15–4.58)	N	N	Y
Card	Palpitations	1.68 (1.06–2.67)			1.99 (1.24–3.2)	N	N	N
Card	Pericardial effusion	2.14 (1.33–3.44)	2.52 (1.44–4.41)		2.05 (1.25–3.37)	N	N	Y
Card	Pericardial haemorrhage	3.03 (1.76–5.23)	2.94 (1.55–5.58)		3.15 (1.8–5.51)	Y	Y	Y
Eye	Blindness	4.51 (1.37–14.83)	5.29 (1.43–19.56)		4.34 (1.28–14.65)	N	N	N
Eye	Eye haemorrhage	1.82 (1.22–2.72)	3.3 (2.12–5.15)	4.74 (1.97–11.41)		Y	Y	Y
Eye	Ocular hyperaemia	3.66 (1.66–8.05)			4.4 (1.99–9.76)	Y	Y	Y
Eye	Retinal haemorrhage	2.37 (1.2–4.67)	4.95 (2.4–10.19)	4.73 (1.03–21.6)		Y	Y	Y
Eye	Vision blurred	1.91 (1.2–3.05)			2.21 (1.37–3.57)	N	N	N
Eye	Visual impairment	4.84 (2.44–9.6)	5.89 (2.8–12.41)	7.89 (2.13–29.17)	4.34 (2.15–8.76)	N	N	N
Gastr	Abdominal discomfort	8.65 (5.78–12.95)		9.51 (4.56–19.85)	11.35 (7.58–17.01)	N	N	Y
Gastr	Abdominal pain upper	5.35 (3.99–7.17)	1.51 (1–2.29)	3.39 (1.53–7.49)	6.91 (5.15–9.28)	Y	N	Y
Gastr	Flatulence	6.74 (4.23–10.73)			9.34 (5.86–14.89)	N	N	N

(continues)

Table 2

(Continued)

MedDRA system organ class[b]	MedDRA preferred term	DOACs ROR	Rivaroxaban ROR	Apixaban ROR	Dabigatran ROR	Notoriety		
						Rivaroxaban	Apixaban	Dabigatran
Gastr	Frequent bowel movements	3.45 (1.56–7.61)			4.7 (2.12–10.38)	Y	Y	Y
Gastr	Gastrointestinal disorder	3.56 (1.9–6.68)			4.24 (2.24–8.01)	Y	Y	Y
Gastr	Gastrointestinal haemorrhage	1.6 (1.47–1.75)	1.38 (1.24–1.55)		1.71 (1.56–1.87)	Y	Y	Y
Gastr	Gastrooesophageal reflux disease	8.68 (4.85–15.53)			11.46 (6.4–20.52)	N	N	Y
Gastr	Haematochezia	1.96 (1.59–2.4)	1.68 (1.29–2.18)		2.11 (1.71–2.61)	Y	Y	Y
Gastr	Haemorrhoidal haemorrhage	3.33 (2.03–5.46)	3.24 (1.82–5.75)	3.94 (1.16–13.4)	3.35 (2.02–5.56)	Y	Y	Y
Gastr	Haemorrhoids	1.89 (1.22–2.94)			2.22 (1.42–3.48)	N	N	N
Gastr	Intestinal haemorrhage	6.24 (3.28–11.88)	10.09 (5.15–19.76)	9.47 (2.97–30.24)	4.66 (2.4–9.05)	Y	Y	Y
Gastr	Intestinal ischaemia	6.04 (2.18–16.73)	3.53 (1.06–11.72)		7.19 (2.58–20.06)	N	N	N
Gastr	Large intestinal haemorrhage	7.98 (2.91–21.89)	3.53 (1.06–11.72)		9.93 (3.61–27.37)	Y	Y	Y
Gastr	Lower gastrointestinal haemorrhage	1.77 (1.39–2.25)	1.73 (1.27–2.34)		1.8 (1.4–2.32)	Y	Y	Y
Gastr	Oesophagitis	2.54 (1.37–4.7)			3.08 (1.65–5.76)	N	N	Y
Gastr	Swollen tongue	2.98 (1.26–7.06)			3.54 (1.48–8.48)	Y	Y	Y
Genrl	Drug ineffective	1.76 (1.35–2.31)	3.84 (2.88–5.12)	3.14 (1.56–6.31)		N	N	N
Genrl	Multi-organ failure	1.99 (1.15–3.44)			2.27 (1.3–3.97)	N	N	N
Genrl	Ulcer	2.9 (1.12–7.47)	3.88 (1.35–11.18)			N	N	Y
Hepat	Acute hepatic failure	4.83 (1.13–20.67)	6.18 (1.28–29.74)		4.45 (1–19.72)	N	N	N
Hepat	Hepatic failure	2.51 (1.28–4.94)	3.88 (1.84–8.21)		2.05 (1–4.2)	N	N	N
Hepat	Hepatic function abnormal	3.38 (1.19–9.64)	4.41 (1.38–14.07)	11.82 (2.16–64.6)		Y	Y[c]	Y
Hepat	Hepatitis	6.04 (1.43–25.5)	10.59 (2.37–47.33)	35.49 (5.93–212.6)		Y	N	N
Infec	Sepsis	1.68 (1.08–2.62)			1.94 (1.23–3.07)	N	N	N
Inj&P	Hip fracture	4.45 (1.77–11.19)			5.48 (2.16–13.88)	N	N	N
Inj&P	Post procedural haemorrhage	1.89 (1.3–2.76)	3.59 (2.38–5.42)			Y	Y	Y
Inj&P	Splenic rupture	3.54 (1.06–11.84)	4.12 (1.06–15.93)			N	N	N
Inv	aPTT prolonged	1.76 (1.26–2.46)			2.26 (1.61–3.17)	Y	Y	Y
Inv	ALT increased	2.33 (1.22–4.46)	5.46 (2.77–10.78)			Y	Y	Y
Inv	AST increased	2.58 (1.26–5.25)	5.89 (2.8–12.41)			Y	Y	Y
Inv	Blood ALP increased	3.58 (1.41–9.1)	7.77 (2.94–20.53)	9.46 (1.83–48.79)		Y	Y	Y

(continues)

Table 2

(Continued)

MedDRA system organ class[b]	MedDRA preferred term	DOACs ROR	Rivaroxaban ROR	Apixaban ROR	Dabigatran ROR	Notoriety		
						Rivaroxaban	Apixaban	Dabigatran
Inv	Blood count abnormal	7.73 (1.02–58.28)	8.82 (1.03–75.52)			Y	Y	Y
Inv	Blood creatinine increased	2.99 (1.99–4.5)	4.13 (2.63–6.48)	5.27 (2.17–12.78)	2.49 (1.62–3.81)	Y[c]	N	N
Inv	Blood glucose increased	3.87 (2.07–7.24)	2.57 (1.19–5.53)	6.45 (1.8–23.16)	4.3 (2.27–8.12)	N	N	N
Inv	Blood urine present	3.13 (2.18–4.5)	4.74 (3.2–7.04)		2.52 (1.72–3.68)	Y	Y	Y
Inv	Haemoglobin decreased	1.25 (1.09–1.44)	2.04 (1.74–2.4)			Y	N	Y
Inv	Heart rate increased	2.65 (1.7–4.13)	1.84 (1.04–3.26)		2.95 (1.87–4.64)	Y	N	N
Inv	Liver function test abnormal	3.06 (1.78–5.28)	6.01 (3.38–10.7)	6.31 (2.09–19.05)	1.83 (1.01–3.31)	Y	Y	Y
Inv	Weight increased	1.8 (1.12–2.88)		5.38 (2.04–14.24)	1.93 (1.19–3.14)	N	N	N
Metab	Decreased appetite	1.39 (1.06–1.84)			1.6 (1.21–2.13)	N	N	N
Metab	Gout	2.78 (1.31–5.89)	3.09 (1.3–7.36)	5.91 (1.25–27.86)	2.57 (1.18–5.6)	N	N	N
Musc	Arthralgia	3.55 (2.72–4.63)	1.6 (1.11–2.29)	3.83 (1.96–7.49)	4.3 (3.29–5.63)	N	N	N
Musc	Arthritis	2.15 (1.12–4.14)		10.77 (3.74–31.05)	2.18 (1.11–4.29)	N	N	N
Musc	Back pain	2.08 (1.49–2.9)		2.75 (1.09–6.96)	2.44 (1.74–3.42)	N	N	N
Musc	Joint swelling	5.81 (3.49–9.68)	2.98 (1.61–5.53)	5.92 (1.98–17.73)	6.91 (4.13–11.55)	Y	N	N
Musc	Muscle spasms	2.4 (1.55–3.72)			2.71 (1.73–4.25)	N	N	N
Musc	Muscular weakness	2.47 (1.53–3.98)	2.83 (1.62–4.94)		2.4 (1.46–3.94)	N	N	N
Musc	Musculoskeletal pain	3.22 (1.6–6.49)			4.11 (2.03–8.32)	N	N	N
Musc	Musculoskeletal stiffness	2.42 (1.01–5.8)		7.88 (1.59–39.08)	2.62 (1.07–6.44)	N	N	N
Musc	Myalgia	2.47 (1.62–3.77)	2.51 (1.52–4.15)		2.45 (1.59–3.79)	N	N	N
Musc	Neck pain	2.52 (1.24–5.15)			3.42 (1.67–7.01)	N	N	N
Musc	Pain in extremity	1.91 (1.5–2.43)	1.7 (1.25–2.32)		1.98 (1.55–2.55)	Y[c]	N	N
Nerv	Basal ganglia haemorrhage	2.66 (1.25–5.65)	6.63 (3.04–14.46)			Y	Y	Y
Nerv	Cerebral infarction	6.82 (3.96–11.72)	6.82 (3.79–12.29)	10.16 (3.9–26.49)	6.72 (3.87–11.64)	N	N	N
Nerv	Cerebrovascular accident	5.19 (4.16–6.48)	6.13 (4.81–7.79)	4.44 (2.59–7.59)	4.85 (3.87–6.09)	N	N	N
Nerv	Embolic stroke	6.63 (3.49–12.6)	5.12 (2.5–10.52)	9.47 (2.97–30.24)	7.13 (3.73–13.65)	N	N	N
Nerv	Haemorrhagic stroke	1.53 (1.12–2.1)	2.28 (1.59–3.27)			Y	Y	Y
Nerv	Haemorrhagic transformation stroke	3.02 (1.05–8.68)	6.62 (2.2–19.95)			Y	Y	Y
Nerv	Hemiparesis	1.47 (1.07–2.02)	3.12 (2.2–4.41)			N	N	N

(continues)

Table 2

(Continued)

MedDRA system organ class[b]	MedDRA preferred term	DOACs ROR	Rivaroxaban ROR	Apixaban ROR	Dabigatran ROR	Notoriety		
						Rivaroxaban	Apixaban	Dabigatran
Nerv	Ischaemic stroke	10.29 (6.02–17.6)	11.14 (6.34–19.59)	6.76 (2.22–20.58)	10.07 (5.86–17.3)	N	N	N
Nerv	Paraesthesia	2.42 (1.56–3.75)	2.65 (1.58–4.44)	4.93 (1.88–12.95)	2.25 (1.43–3.56)	N	N	N
Nerv	Speech disorder	2.6 (1.22–5.52)	5.3 (2.38–11.8)			N	N	N
Nerv	Transient ischaemic attack	3.11 (2.25–4.31)	3.2 (2.2–4.67)	5.66 (2.83–11.31)	3.01 (2.15–4.21)	N	N	N
Renal	Chromaturia	2.51 (1.45–4.37)	3.41 (1.83–6.37)		2.24 (1.25–3.99)	N	N	N
Renal	Nephrolithiasis	2.06 (1.07–3.98)	2.41 (1.11–5.24)			N	N	N
Renal	Pollakiuria	4.14 (1.89–9.06)			5.68 (2.59–12.44)	N	N	N
Renal	Renal failure	2.91 (2.09–4.05)	2.8 (1.9–4.15)		2.98 (2.12–4.19)	Y	N	N
Renal	Renal failure acute	1.84 (1.46–2.3)			2.06 (1.63–2.6)	Y	N	N
Renal	Renal impairment	4.66 (2.91–7.48)	6.06 (3.63–10.1)		4.22 (2.6–6.86)	Y	N	N
Renal	Urinary bladder hemorrhage	3.69 (1.76–7.7)	8.62 (4.03–18.45)			Y	Y	Y
Resp	Pulmonary embolism	6.03 (3.73–9.75)	7.28 (4.35–12.19)	6.58 (2.44–17.75)	5.53 (3.39–9.02)	N	N	N
Resp	Pulmonary haemorrhage	2.07 (1.29–3.33)	2.27 (1.28–4.02)		2.02 (1.23–3.32)	Y	Y	Y
Skin	Pruritus	1.63 (1.3–2.04)	1.4 (1.04–1.89)	3.19 (1.78–5.7)	1.67 (1.32–2.11)	Y	Y	Y
Skin	Pruritus generalised	3.52 (1.87–6.6)	3.53 (1.71–7.28)	6.45 (1.8–23.16)	3.42 (1.79–6.54)	Y	Y	Y
Skin	Rash	1.31 (1.04–1.64)		2.8 (1.53–5.1)	1.44 (1.14–1.83)	Y	Y	Y
Skin	Rash generalised	2.15 (1.04–4.43)		7.89 (2.13–29.17)	2.21 (1.04–4.66)	Y	Y	Y
Skin	Skin haemorrhage	4.06 (2.11–7.82)	7.43 (3.73–14.8)	4.73 (1.03–21.6)	2.74 (1.37–5.48)	Y	Y	Y
Skin	Swelling face	3.14 (1.49–6.61)			3.85 (1.82–8.17)	Y	Y	Y
Skin	Urticaria	2.29 (1.46–3.59)			2.56 (1.62–4.06)	Y	Y	Y
Vasc	Deep vein thrombosis	4.73 (3.02–7.41)	6.83 (4.23–11.05)	6.77 (2.73–16.81)	3.85 (2.42–6.13)	N	N	N
Vasc	Thrombosis	2 (1.39–2.88)	3.24 (2.16–4.87)	3.95 (1.66–9.39)		N	N	N

MedDRA, Medical Dictionary for Regulatory Activities; DIC, disseminated intravascular coagulation; aPTT, activated partial thromboplastin time; ALT, alanine aminotransferase; AST aspartate aminotransferase; ALP, alkaline phosphatase

[a]Empty cells indicate absence of statistical association (ROR (–) ≤1, $P > 0.05$) or inverse disproportionality (ROR <1, $P \leq 0.05$)

[b]MedDRA System organ classes: Blood and lymphatic system disorders, Cardiac disorders, Eye disorders, Gastrointestinal disorders, General disorders and administration site conditions, Hepatobiliary disorders, Infections and infestations, Injury, poisoning and procedural complications, Investigations, Metabolism and nutrition disorders, Musculoskeletal and connective tissue disorders, Nervous system disorders, Renal and urinary disorders, Respiratory, thoracic and mediastinal disorders, Skin and subcutaneous tissue disorders, Vascular disorders

[c]Observed in prevention of venous thromboembolism in adult patients undergoing elective hip or knee replacement surgery

dose regimen or in a possible instability of plasma concentration of drugs [13].

According to a US study [14], and the dabigatran RE-LY study, older age (≥75 years) seems related to a greater decrease of DOACs clearance compared to warfarin, which can lead to an increased gastrointestinal bleeding risk [29].

Based on those studies, the population average age in our analysis (75.6 years) is consistent with the very high rate of gastrointestinal bleeding events, thereby straightening the reliability of our results.

Apixaban was not associated with gastrointestinal bleeding as already highlighted by the ARISTOTLE trial [6], and by the meta-analysis performed by Holster *et al*. [30]. Hence, our results indicate apixaban as a possible first line treatment in patients with risk factors for gastrointestinal haemorrhage.

Cases concerning cardiovascular and systemic disorders were detected, in particular dabigatran-associated myocardial infarction (MI) and acute myocardial infarction; evidence of this potential association already emerged from the RE-LY pre-authorization trial [5] and other studies [15, 16, 31], although results did not always achieve statistical significance [12, 32]. We observed an increased risk of MI associated with rivaroxaban, which is not acknowledged in SmPCs. Again, apixaban had no statistical association with MI. Artang *et al*. showed no difference in the rate of MI among warfarin versus factor Xa inhibitors users [16]; conversely, very recent studies conclude that only dabigatran has some evidence of cardiovascular risk, not supporting potential increased MI risk with direct Xa factor inhibitors [33, 34]. In addition, it has to be borne in mind that in our analysis we have not accounted for patients' underlying diseases, although AF is a known risk factor for MI.

According to Caldeira *et al*., current evidence does not exclude the use of any DOAC in patients with AF for the prevention of acute coronary events [34]. However, further efforts need to be made in order to clarify the comparative coronary safety of DOACs.

Statistical analysis highlighted a positive association with angina pectoris for both rivaroxaban and dabigatran; this ADR is acknowledged in rivaroxaban SmPCs, but not in that of dabigatran.

In our research, all DOACs were significantly associated with cardiac failure in both the overall and the individual analysis; nonetheless, it has to be underlined that AF is present in 20–52% of patients with heart failure, and *vice versa*, hence the onset of these cardiac disorders is strictly connected [35].

We reported a notable number of strokes and thromboembolic events, which resulted statistically significant for all DOACs compared to warfarin; in addition, dabigatran was statistically associated with disseminated intravascular coagulation. The assessment of these adverse events is complicated for the following reasons: firstly, data from literature do not support this possibility, since in meta-analyses and in Phase III trials, DOACs showed reduced risk of stroke and systemic embolism compared to warfarin [9]. Moreover, AF is a noteworthy risk factor for stroke and all-cause mortality, particularly in older people [36]; and finally, we lack information about patients' clinical status, comorbidities and possible drug interactions.

Another aspect we evaluated in our study is the potential DOACs induced liver injury.

Possible onset of hepatitis is already known for rivaroxaban only [37], while no mention about occurrence of hepatic failure is reported in SmPCs of the three drugs. Among novel anticoagulants, rivaroxaban is in part metabolized by the liver, while liver excretion represents a minor elimination pathway for apixaban and is negligible for dabigatran. Our results were reliable, as rivaroxaban was responsible for the majority of hepatic disorders and a significant disproportionality for rivaroxaban-associated hepatitis was detected, despite the small number of cases. Rivaroxaban was also associated with hepatic failure, as well as dabigatran, even though the statistical significance of the latter was almost negligible.

As for apixaban, very few cases of hepatitis were retrieved from VigiBase and the statistical analysis, albeit significant, showed a too large CI to allow any consideration.

Some clinical trials described rare cases of DILI with DOACs; however, DOACs induced liver injury is considered an idiosyncratic reaction, therefore insufficient number of patients, exclusion criteria such as pre-existing liver disease and short duration of treatment, make it difficult to provide reliable data in the premarketing phase [18]. Case reports regarding rivaroxaban have been already published [38–42].

Our findings confirm the evidence of a potential higher risk of liver damage with rivaroxaban relative to other anticoagulants; based on current data, it seems appropriate to straighten the recommendation to avoid rivaroxaban prescription in patients with hepatic diseases or with risk factors for liver injury.

Many other potential signals emerged, which are worthy of discussion, as they can negatively influence patient's compliance.

We retrieved a very high number of musculoskeletal disorders associated with all DOACs, and dabigatran was the most reported. Almost the totality of musculoskeletal disorders we have identified are not yet acknowledged, with exception for rivaroxaban. No information about such associations emerged from literature.

Dabigatran was statistically associated with hip fracture: only one case report from Denmark described an 82-year-old women who experienced hip fracture while on treatment with dabigatran etexilate [43]. An *in vitro* study about rivaroxaban effect on bones highlighted an important reduction of osteoblast functions, expressed through the reduction of alkaline phosphatase and reduced expression of the bone marker, osteocalcin, the major osteoblast factor, Runx2, and the osteogenic factor, BMP-2 [44].

Data from literature are too unreliable to make any hypothesis on a possible class effect that could straightens this association; however, considering the connection between fractures and fall-associated injuries such as the risk of haemorrhage, our findings suggest further assessments on the potential occurrence of musculoskeletal disorders and injuries.

Many cases of renal failure after use of dabigatran and rivaroxaban were detected; for both drugs, disproportionality analysis confirmed the potential association. Only rivaroxaban SmPCs report renal failure as a possible adverse effect.

Renal function is a parameter that should be monitored by physician when an anticoagulation treatment is started; indeed, patients with AF have higher than normal risk for renal damage [45] and renal impairment represents an independent risk factor for haemorrhage. DOACs have a predictable pharmacokinetics; however, some authors have suggested that plasma concentration of DOACs is subjected to variations from one patient to another [13].

Since renal damage could worsen this pharmacokinetic parameter by decreasing drug clearance, we believe that monitoring of renal function and plasma concentration, fixing dosage for patients who are at greater risk of renal failure, would be beneficial.

Our analysis highlights a potential signal of dabigatran-associated renal failure, which should be further evaluated. On the contrary, as well as other studies did [36], we found that apixaban could be the drug of choice in subjects with AF who have a higher risk of renal damage, as in our analysis it was not associated with renal damage and it is mostly excreted through the biliary route.

Overall, our study on DOACs' postmarketing safety data pointed out a large number of ADRs and potential new safety signals associated with dabigatran and rivaroxaban, in particular; apixaban seems to have a better safety profile of the novel anticoagulants we analysed.

In evaluating these findings, some crucial points need to be considered. Firstly, dabigatran and rivaroxaban received the first European marketing authorization in 2008, while apixaban received it only in 2011. Secondly, dabigatran was the first DOAC released on the market for patients with AF in daily clinical practice. Besides, during recent years, regulatory agencies have published a great number of safety alerts referred to dabigatran and many studies have focused their attention on the safety profile of the thrombin direct inhibitor; therefore, data from postmarketing practice may have been influenced by this context [46].

A limitation of some novel anticoagulants is represented by the absence of a specific antidote; however, in November 2015 the European Medicines Agency approved the dabigatran reversal agent, idarucizumab. A specific antidote for factor Xa direct inhibitors is still under investigation.

Our study has some limitations. The analysis was performed on data from a global spontaneous reporting system, which may have not included consecutive cases, as treatment allocation is not randomized and missing data on reports may occur. Postmarketing data may be subject to biases such as stimulated reporting, selective reporting and under-reporting [47, 48], as only 10% of all ADRs are actually reported [48].

Also, we did not account for populations differences across countries, which can interfere with the robustness of the observed associations, as incidence and prevalence rates of diseases may differ.

Another limitation is that clinical information contained in a spontaneous reporting database such as WHO VigiBase is limited. Some of the evaluated cases might have been affected by predisposing disorders or concomitant medications, as our population study were the elderly, who are more likely to suffer from different serious medical conditions, and we could not assess the medical history of patients. In addition, AF represents an independent risk factor for many diseases. Therefore, data do not allow any conclusions on causality between exposure and ADRs to be drawn.

Another element to consider is that we classified ADRs with MedDRA Preferred Term, which represents a specific level of MedDRA hierarchy; this specificity may cause conflicting statistical measurements, because similar conditions may be identified with different terms. Considering a higher level of MedDRA hierarchy such High Level Term or the grouped Standardized MedDRA Queries, would have avoided this limitation; however, this approach allowed us to be more accurate from a clinical point of view, extracting from VigiBase a higher number of reactions.

Pharmacovigilance databases can be redundantly reported, although our method allowed us to eliminate as much as possible potential duplicates.

Lastly, ROR computing does not allow quantification of the true risk of ADR; it only suggests a statistically significant association between a drug and an adverse event, which should be further investigated.

Advantages are that VigiBase covers patients from most countries worldwide and reports contained therein reflect real-life events, and therefore may comprise drug-use patterns that cannot be studied in clinical trials for ethical reasons, such as elderly or paediatric population, excessive dosage and inappropriate comedication.

Conclusion

Studies based on spontaneous ADR reporting represent an essential and irreplaceable source for the identification of new potential ADRs.

Regarding the comparative safety profile of DOACs vs warfarin, our study is coherent with results from pre- and postmarketing clinical trials, even though we identified some new potential safety signals, for which further in-depth analysis should be performed.

Overall, our data showed that DOACs were associated with a lower risk of cerebral haemorrhage, but with an increased risk of gastrointestinal bleeding, myocardial infarction (dabigatran and rivaroxaban) and liver injury (rivaroxaban) against warfarin.

Moreover, the analysis suggests that DOACs are not interchangeable, as several differences emerged in the rate and type of ADRs between one drug and another. These differences must be carefully evaluated by physicians, on the basis of patient characteristics and medical history, in order to prescribe the most appropriate drug.

Our data support the better safety profile of apixaban compared to other DOACs. Nevertheless, apixaban is one of the most recent marketed oral anticoagulant, and further analyses are needed.

Our analysis highlights that rare but serious ADRs can be detected only after marketing authorization. These safety signals require follow-up by regulatory authorities.

Competing Interests

There are no competing interests to declare.

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Luca Monaco and Domenico Motola had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Contributors

Substantial contributions to conception or design of the work (L.M., D.M., C.B., M.D., M.M.), or the acquisition (A.V., M.V., V.C.), analysis (L.M., V.C., M.M., M.D., C.B.) or interpretation of data for the work (D.M., M.V., A.V.); Drafting of the work (L.M., C.B., D.M., M.M., M.D.) or revising it critically for important intellectual content (M.V., V.C., A.V.); All the authors approved the submitted final version to be published; All the authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supporting Information

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Table S1 Distribution of seriousness criteria (as indicated into the Individual Case Safety Report) related to age category and sex
Table S2 Number of cases of adverse drug reactions (with reporting odds ratio >1, $P \leq 0.05$) associated with rivaroxaban
Table S3 Number of cases of adverse drug reactions (with reporting odds ratio >1, $P \leq 0.05$) associated with apixaban
Table S4 Number of cases of adverse drug reactions (with reporting odds ratio >1, $P \leq 0.05$) associated with dabigatran
Table S5 Number of cases of adverse drug reactions associated with direct oral anticoagulants (reporting odds ratio >1, $P \leq 0.05$) compared to warfarin
Table S6 Adverse drug reactions associated with direct oral anticoagulants with inverse disproportionality (reporting odds ratio <1, $P \leq 0.05$ and at least 10 cases)